Leadership for HIV/AIDS Clinical Trials Networks Pre-Application Meeting

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DAIDS mission is to help end the HIV/AIDS pandemic

……..by supporting research to increase the basic knowledge of the pathogenesis and transmission of HIV in order to develop therapies for HIV infection and its complications, and develop vaccines and other prevention strategies.

Current DAIDS Clinical Trials Networks

AACTG – est. 1987

PACTG – est. 1993

CPCRA – est. 1993

AIEDRP – est. 1997

ESPRIT – est. 1999

HVTN – est. 2000

HPTN – est.2000

USMHRP – linked 2001

Phidisa – est. 2002

CDC – linked 2003

The Networks are not the only game in town; clinical research is also supported by other funding mechanisms:

- RO1
- PO1
- CIPRA
- CFAR

Selected Network Accomplishments

- establishment of critical databases for continued clinical research
- instrumental in establishing expertise in HIV/AIDS clinical research
- research underpinned the establishment of treatment guidelines
- established interruption of MTCT
- underpinned the remarkable decreased mortality rates in HIV infected adults, adolescents and children
- advanced treatment and prevention of OIs
- development of immune-based therapies
- development of global infrastructure for HIV vaccine and prevention clinical research

Network Accomplishments- con't

Number of publications since 1987:

over 1800

So why the Re-structuring?

“In life, one thing is absolutely inevitable - continuous change”

Randall Tobias

The State of the Pandemic

The HIV/AIDS pandemic continues to expand at an extraordinary rate with continuing unacceptable individual, social, political impacts.

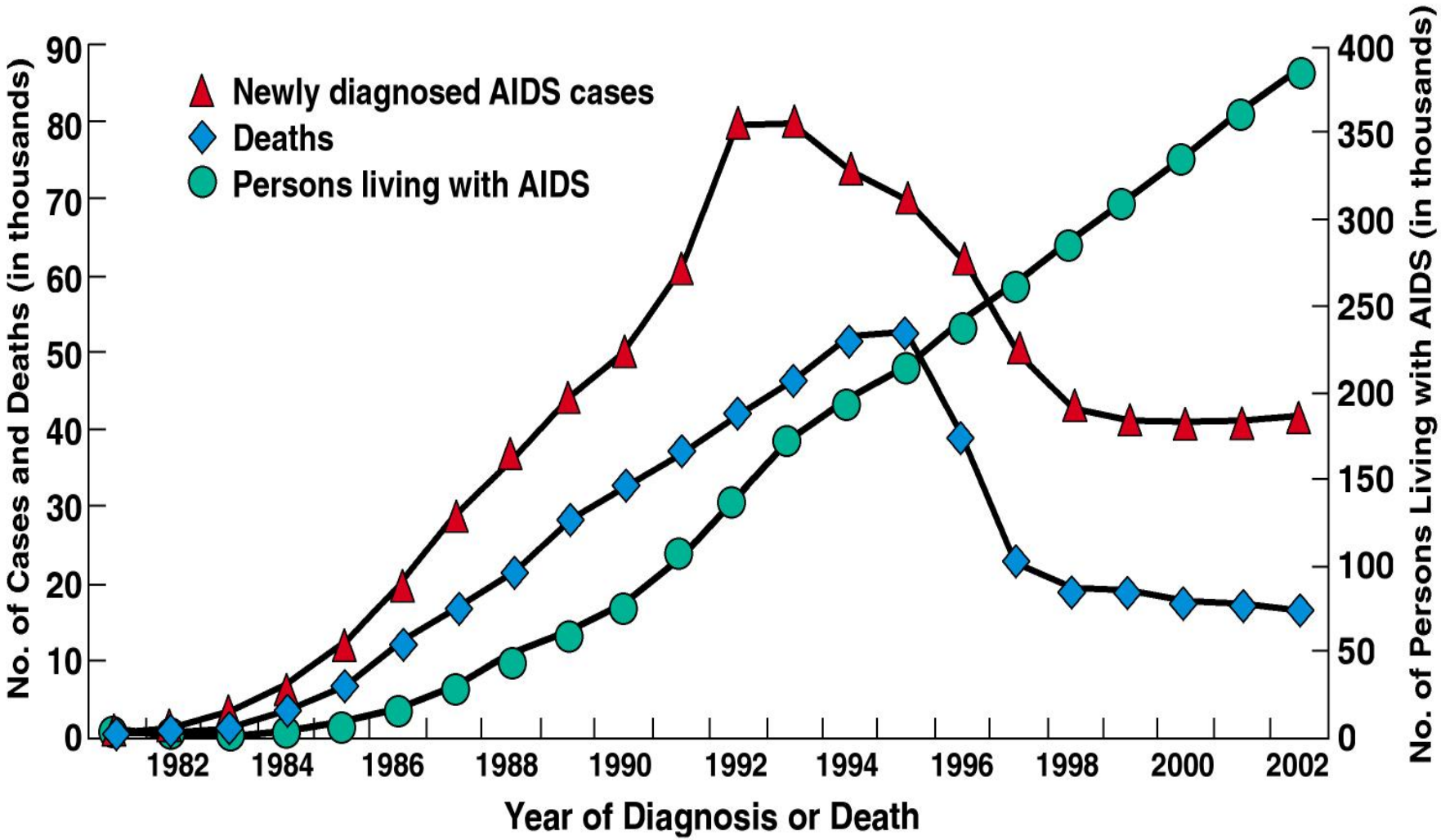
Global HIV/AIDS Estimates December, 2003

People living with HIV/AIDS	40 million (34 - 46 million)
New HIV infections in 2003	5 million (4.2 - 5.8 million)
Deaths due to HIV/AIDS in 2003	3 million (2.5 - 3.5 million)

Source: UNAIDS

Impact of HAART

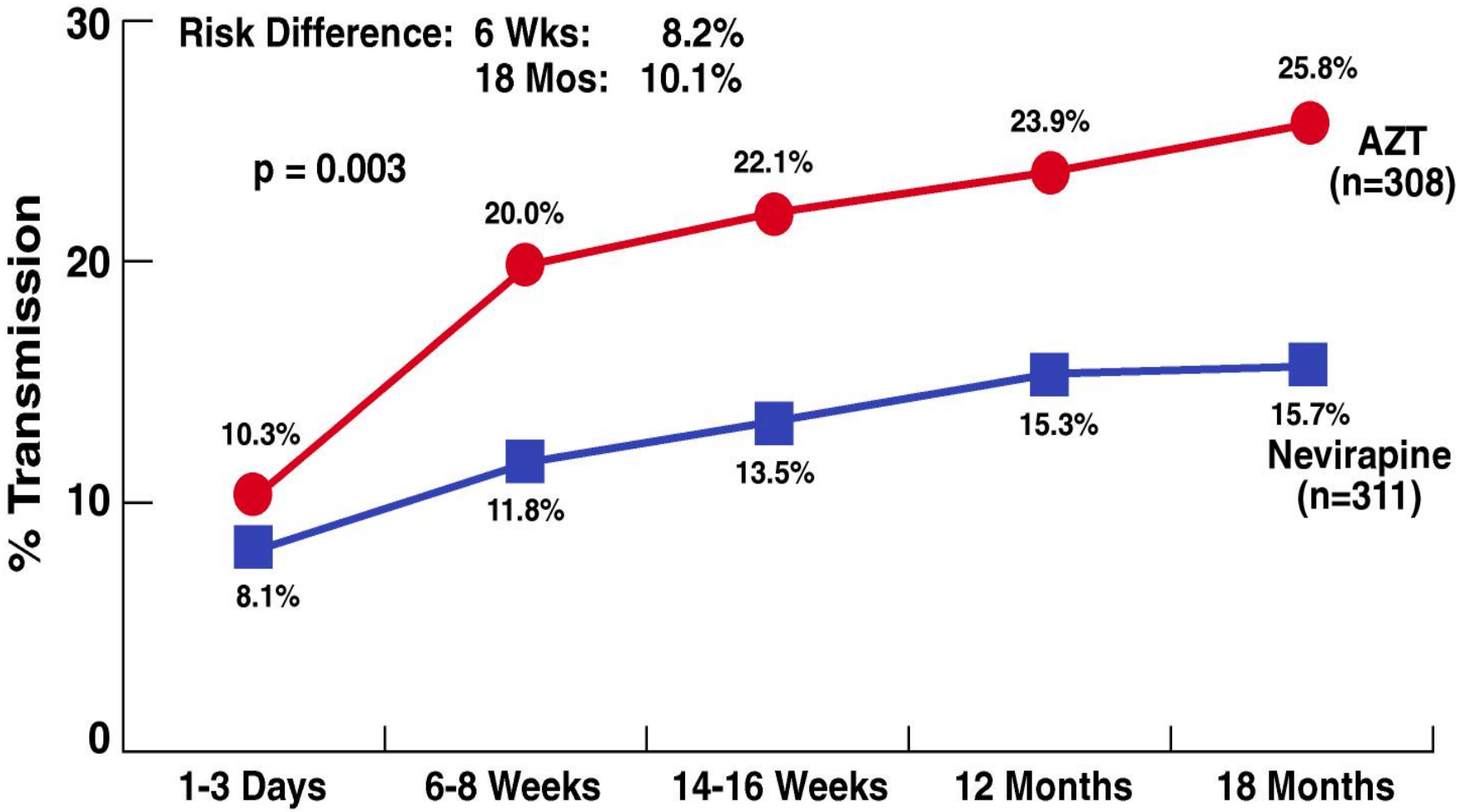
AIDS Cases, Deaths, and Persons Living with AIDS, United States, 1981-2002



Adjusted for reporting delays

Source: CDC

HIVNET 012: 18-Month Follow-up



Jackson JB et al. *Lancet* 9/13/2003.

But at a price (legacy of HAART)

Changes the characteristics of the disease

- **associated with an increased incidence of end-stage liver disease (HCV, HBV)**
- **associated with an increased incidence of end-stage renal disease**
- **associated with increase in viral associated cancers**

  e.g. non-Hodgkin's lymphoma,

  cervical cancer, other cancers

Associated with increased HIV resistance

Associated with adverse affects with long-term use – “The Vioxx Effect”

Time to Death

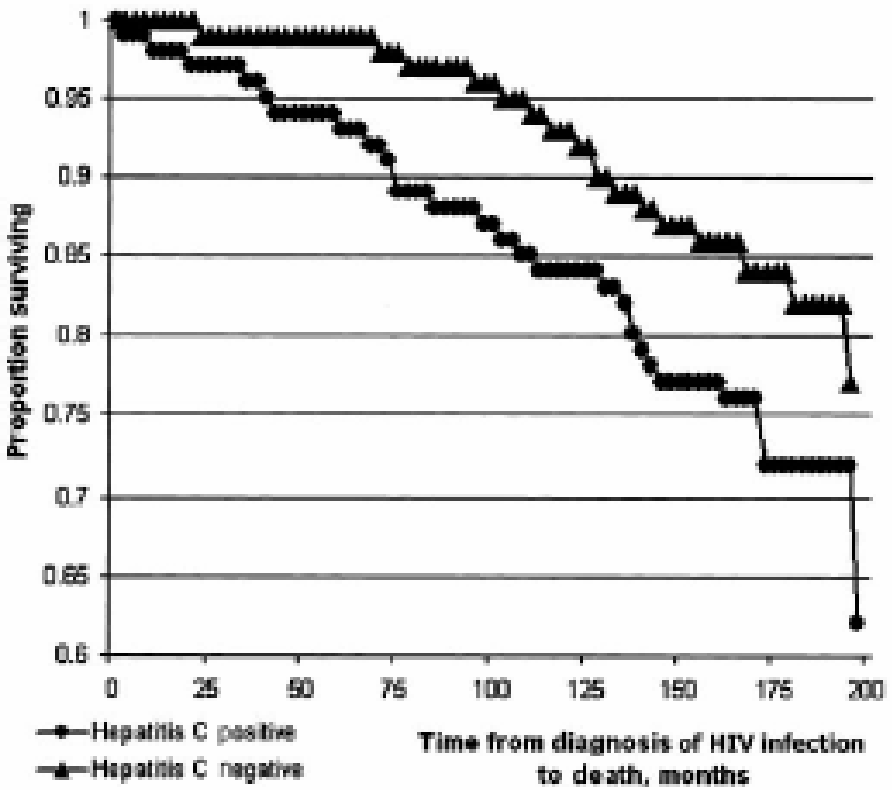
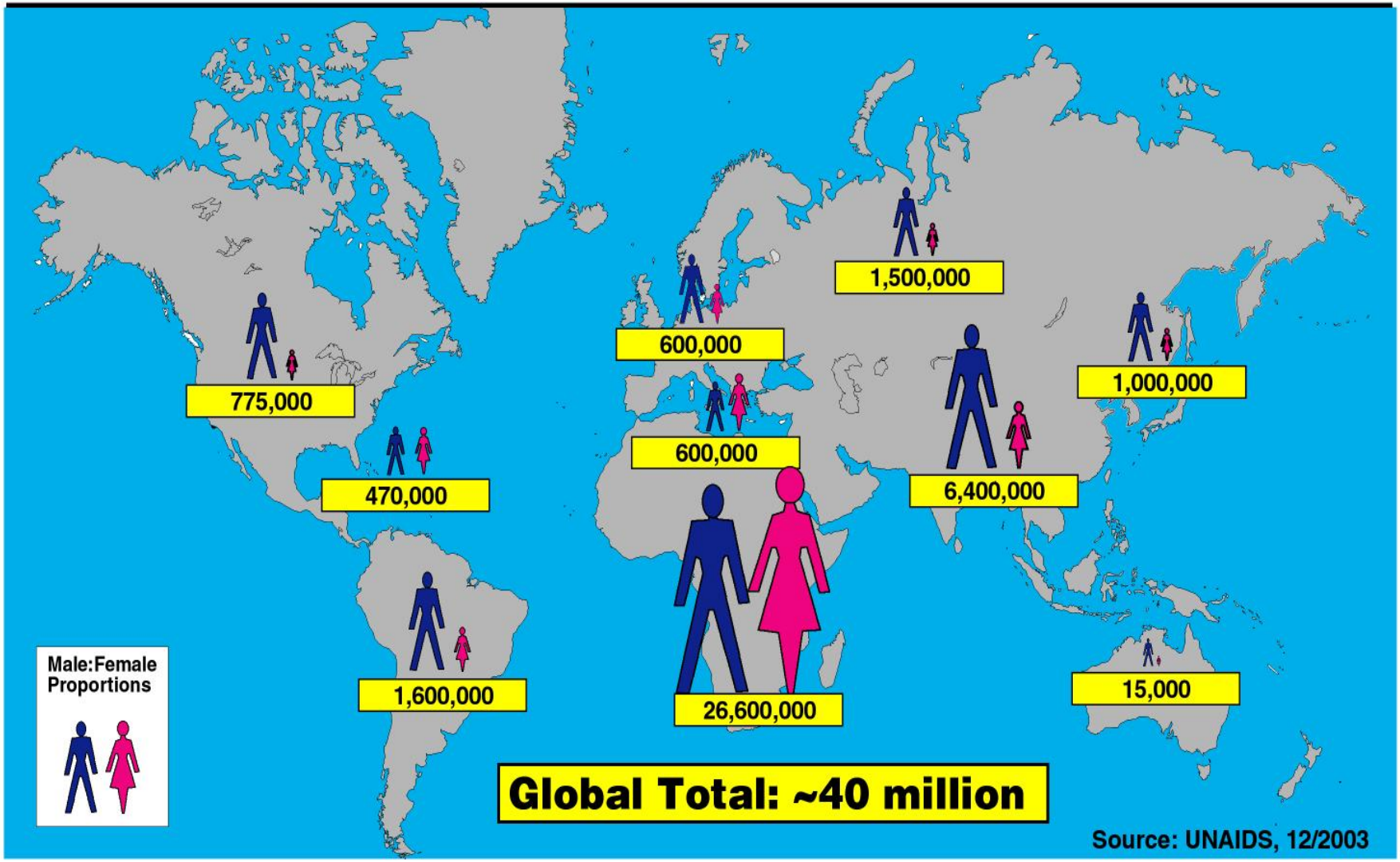


Figure 1. Survival curve for time from diagnosis of HIV infection to death, stratified by hepatitis C virus coinfection status and adjusted for $CD4^+$ cell count, race, age, AIDS diagnosis, HAART use, history of hepatitis B virus infection, and risk factor for HIV infection.

Source: CID 2004; 39:1511

Impact in Resource Limited Settings

Estimated Number of Persons Living with HIV/AIDS, December, 2003

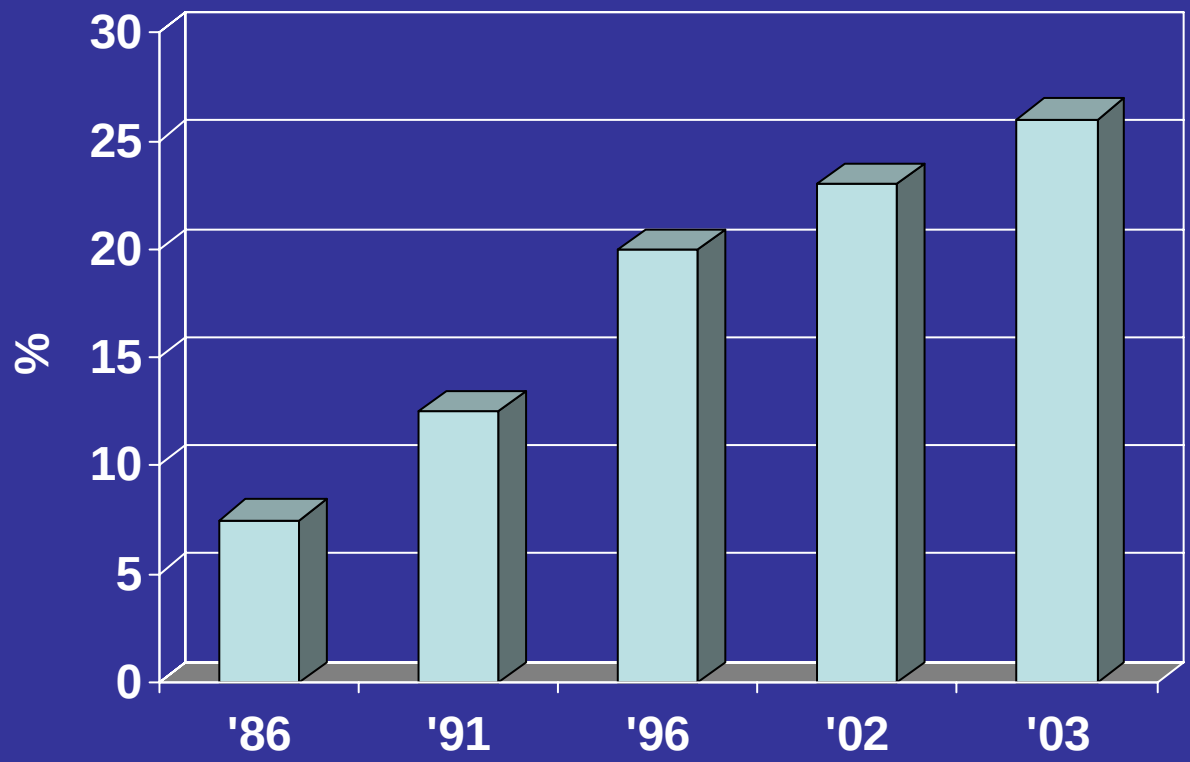


Changing Dynamics of the Epidemic in the USA

Women

Minorities

HIV Rates in Women - USA



HIV/AIDS in Blacks and Hispanics USA

- 58% of total
- 78% of women
- 79% of infected heterosexuals
- 82% of children
- 68% of adults and adolescents

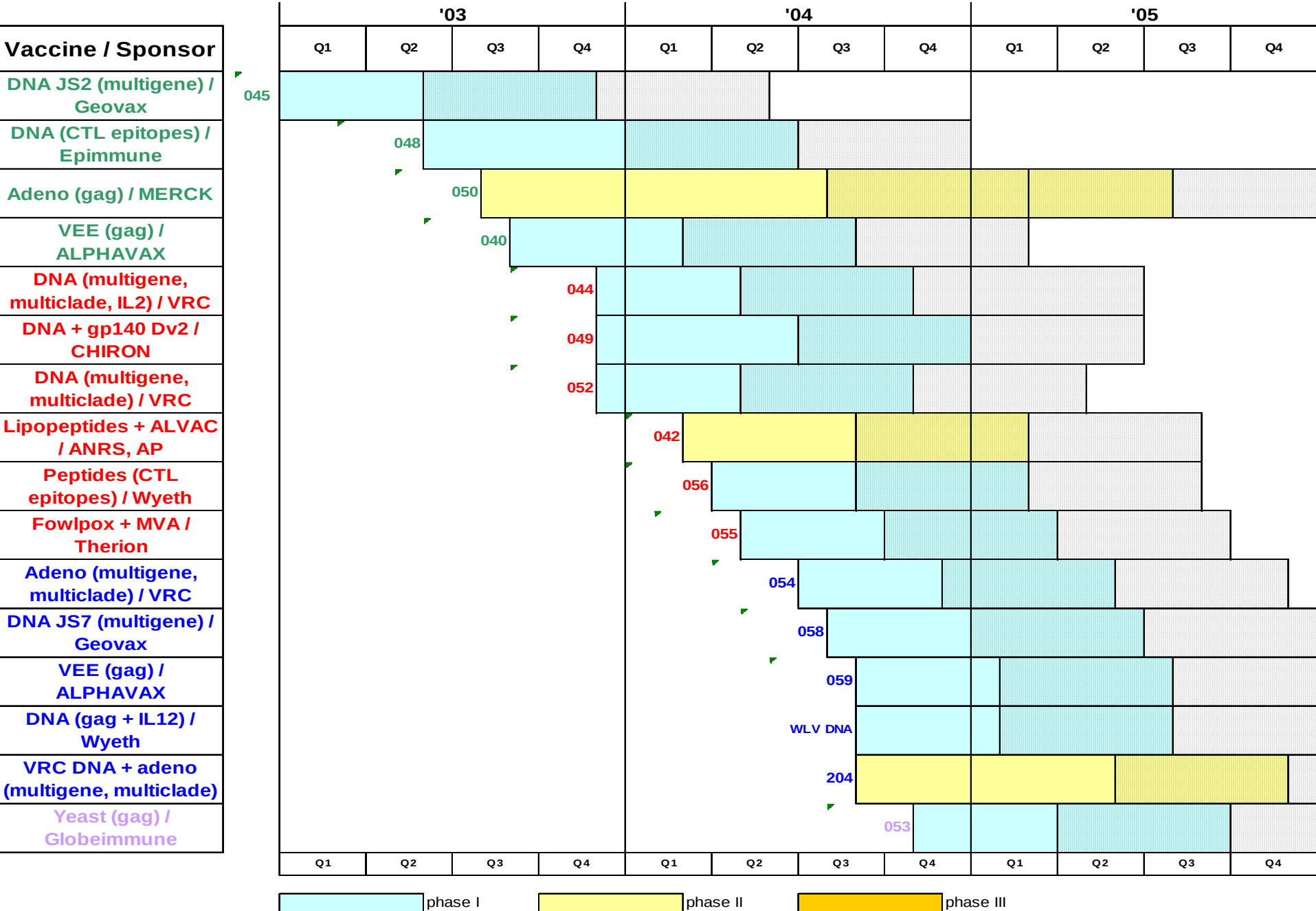
CDC 2002

Continued Beneficial impacts of the ongoing research on clinical research

Vaccine Candidates in Phase I/II Trials

- DNA vectors
  - DNA-polyepitope-gag (C) (IAVI/Oxford/Kenya/Uganda)
  - DNA-gag-pol,nef; env (A,B,C) (NIAID VRC)
  - DNA-multi-gene (B) (Emory/GeoVax/CDC/NIAID)
  - DNA-multigene (C) (EuroVacc)
  - DNA-multi-epitope (Ep immune/NIAID)
  - DNA multigene (C) (Aaron diamond)
  - DNA+adeno (A,B,C) (NIAID/VRC)
- Viral vectors and combinations
  - Adeno-gag; pol; nef (B) (Merck) +/- ALVAC boost (AvP)
  - Adeno-env,gag,pol (A,B,C) (NIAID VRC)
  - VEE-gag (C) (AlphaVax/NIAID/IAVI)
  - Adeno-associated Virus (C) (Targeted Genetics/IAVI)
  - NYVAC (C) (EuroVacc)
- DNA Combinations
  - DNA + MVA, multi-epitope + gag (A) (IAVI)
  - DNA + FP multi-gene (B) (UNSW/NIAID)
  - DNA-env + Env (B) (Chiron/NIAID)
- Other
  - Tat-nef +/- gp120 in AS02-A (B) (SKB)
  - Tat (ISS)
  - ALVAC + Lipopeptides (B) (ANRS, AvP, NIAID)

HVTN / DAIDS PROTOCOLS 2003-2004



Microbicides

- In development:
  - UC781 (NNRTI)
  - Cyanovirin (entry inhibitor)
  - PSC- Rantes
  - VivaGel + BufferGel
  - Engineered Lactobacillus expressing cyanovirin, CD4, single chain anti-ICAM antibodies or Rantes peptides
- Phase I evaluation:
  - VivaGel (SPL7013 from StarPharma Ltd)
  - Cellulose Acetate Phthalate (CAP)
  - Polystyrene sulfonate (PSS)
  - Acidform
- Phase II evaluation:
  - Tenofovir Gel (HPTN 059)

nature medicine

Therapeutic dendritic-cell vaccine for chronic HIV-1 infection

Wei Lu, Luiz Claudio Arraes,Wylla Tatiana Ferreira, Jean-Marie Andrieu

“immunized 18 chronically HIV-1-infected and currently untreated individuals with autologous monocyte-derived DCs loaded with autologous aldrithiol-2-inactivated HIV-1. Plasma viral load levels were decreased by 80% (median) over the first 112 d following immunization. Prolonged suppression of viral load of more than 90% was seen in 8 individuals for at least 1 year.

The results suggest that inactivated whole virus–pulsed DC vaccines could be a promising strategy for treating people with chronic HIV-1 infection.”

Oct 2004

Impact of a Stable budget

At best, a Stable budget is predicted

- Need for improved efficiency
- Need for improved flexibility
- Need (opportunity) for establishing new collaborations
- Need to cover the “out years”
- Need to be able to address a fluctuating dollar vs. other currencies

Consultations

From October 2001 through November 2004 (36 months), there have been 63 consultations with network leaders and scientists, non-network clinicians and scientists, other NIH Institutes, other federal agencies, the ARAC, community organizations and people living with and at risk for HIV/AIDS

What we heard/learned

Benefits

- **Peer-review hones ideas which improves research quality**
- **Brings together expert investigators in collaborative/cooperative groups**
- **Provides continuity for strategic planning and product development**
- **“Re-usable” infrastructure promotes efficiency, data quality & comparability**

What we heard/learned

Challenges

- **Networks function in isolation from one another, although this has been addressed recently**
- **Other**

Leadership RFA Goal

Address the clinical research questions of highest priority in prevention, in treatment, across-networks, across Institutes, in all countries, in all populations, with appropriate products, with any credible partners.

Scientific Objectives

(1) Vaccine Research and Development;
(2) Translational Research/Drug Development;
(3) Optimization of Clinical Management, Including Co-Morbidities;
(4) Microbicides;
(5) Prevention of Mother-to-Child Transmission (MTCT) of HIV;
(6) Prevention of HIV Infection.

Operational Objectives

- maximize scientific opportunities through coordinated and collaborative research that leverages complementary strengths and resources both within and outside the networks
- improve efficiency and cost effectiveness through resource sharing
- build and sustain clinical research capacity, including in resource poor settings
- improve evaluation/review to ensure that highest research priorities are addressed in a timely manner

NIH Science is

hypothesis generated, protocol driven research

“Without a shared vision that is compelling and truly embraced with passion, it is nearly impossible for any organization to be successful.”

Randall Tobias